REMARKS

I. Pending Applications

For the convenience of the Examiner, the following co-pending U.S. Applications are related:

09/386,591 (this pending application)

08/934,367, filed 09/19/97 (parent application, pending in Group Art Unit 1642, Examiner Minh-Tam Davis, cited in paper number 4, the Office Action dated 5/22/00 of this pending application)

08/788,882, filed 01/21/97 (parent application, pending in Group Art Unit 1642, Examiner Minh-Tam Davis)

08/785,997, filed 01/21/97 (parent application, pending in Group Art Unit 1642, Examiner Minh-Tam Davis)

For the further convenience of the Examiner, the following co-pending U.S. Application may be of relevance:

09/387,340, filed 08/31/99 (pending in Group Art Unit 1642, Examiner Minh-Tam Davis)

II. Status of the Pending Claims

Claims 3-7, 12, 13 and 22-39 and newly added claims 40-47 are pending in the instant application.

Claims 3, 6, 7, 26, 29, 30 and 34-36 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Thomas et al. in view of Francis and Clarke.

Claims 4, 5, and 37-39 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Thomas et al. in view of Francis and Clarke and further in view of Donnelly et al.

Claims 12, 13, and 32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Thomas et al. in view of Brown et al.

Claims 22, 25, 27, 28, 31 and 33 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Finally, claims 3-7, 12, 13 and 22-39 stand rejected under the judicially created doctrine of obviousness-type double patenting over copending Application serial number 08/934,367 (claims 2-7, 8-11 and 15-31). Claims 23 and 24, are subject only to this double patenting rejection.

III. Claims Rejected Under 35 U.S.C. § 103

Claims 3, 6, 7, 26, 29, 30 and 34-36 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Thomas et al. (J. Allergy Clin. Immunol., vol. 99, no. 1, p. S187, January 24, 1997) in view of Francis and Clarke (Methods in Enzymology, vol. 178, pp. 659-676, 1989). Claims 4, 5, and 37-39 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Thomas et al. in view of Francis and Clarke and further in view of Donnelly et al (J. Immunological Methods, vol. 176, No. 2, pp. 145-152, 1994). Claims 12, 13, and 32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Thomas et al. in view of Brown et al. Applicants respectfully traverse this rejection.

A. The Affidavit Under 37 CFR § 131 Previously Filed in the Instant Application

It is noted that the previously filed affidavit under 37 CFR § 1.131 was accepted by the Examiner to overcome the initial rejection under 35 U.S.C. § 103. However, the

examiner has stated that the 131 affidavit is not effective to overcome the instant references directed to DNA vaccination.

The Examiner points to Eck and Wilson, in the 9th edition of Goodman and Gilman's The Pharmacological Basis of Therapeutics (1996 pages 77-101) as support for the contention that peptide vaccines are not predictive of administration of a DNA vaccine. Specifically, the basis for the Examiner's assertion is that:

> " the considerations necessary for a successful DNA vaccine are different from what is required for a peptide vaccine. Factors to be considered include: distribution of the DNA vector, the fraction of the vector taken up by the target cell population, the intracellular trafficking, rate of degradation of DNA, mRNA stability, and compartmentalization and secretion of the expressed protein [Eck and Wilson, in the 9th edition of Goodman and Gilman's The Pharmacological Basis of Therapeutics (1996 page 82)].

However, a careful reading of Eck and Wilson, in the 9th edition of Goodman and Gilman's The Pharmacological Basis of Therapeutics (1996 pages 77-101), reveals that the particular technology described at page 82 is under the heading *gene transfer*. In other words, the problems associated the insertion of a new gene that "ultimately corrects a deficiency" (Eck and Wilson, page 78) are subject to the potential problems pointed out by the Examiner. However, the instant application is not directed to the treatment of an inherited disease via gene replacement, but rather to immunizations against a self protein.

In contrast, the *Donnelly* reference (cited by the Examiner as making the claims of the present invention obvious) concludes that "Immunization with DNA is a simple, robust, and effective means of eliciting both antibody and cell-mediated immune responses." And that "... the present experience indicates that DNA immunization is a

useful method of raising immune responses, including monoclonal antibodies, against viral proteins, immunoglobulins, and other antigens of immunological interest."

Moreover, Applicant's claimed DNA vaccine encodes the same peptide antigens as are disclosed in Applicant's earlier-filed applications. Therefore, contrary to the Examiner's contention, a peptide immunogen, and specifically the CETP peptide immunogens of the instant invention, *are* predictive of a DNA vaccine.

B. The *Prima Facie* Case of Obviousness Under 35 U.S.C. § 103

A claimed invention is unpatentable for obviousness if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a) (1994); *Graham v. John Deere Co.*, 383 U.S. 1, 14, 148 USPQ 459, 465, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966). Obviousness is a legal question based on underlying factual determinations including: (1) the scope and content of the prior art, including what that prior art teaches explicitly and inherently; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness. *Graham*, 383 U.S. at 17-18, 148 USPQ at 467; *In re Dembiczak*, 175 F.3d 994, 998, 50 USPQ 1614, 1616 (Fed. Cir. 1999); *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) (stating that the inherent teachings of a prior art reference is a question of fact).

The Thomas reference implies that two regions of rabbit CETP are necessary for the DNA vaccine described therein. However, the Thomas reference does not specify *which* two regions were used. Nor does the Thomas reference teach *where* the two

regions of rabbit CETP were attached to the tetanus toxoid fragment. Nor does the Thomas reference teach *how long* the respective rabbit CETP regions, the tetanus toxoid fragment, and the entire peptide was. In fact, the Thomas reference does not teach anyone of ordinary skill in the art how to construct the DNA vector that was allegedly used. None of the secondary references supplement Thomas to provide an enabling disclosure sufficient to teach one of ordinary skill in the art how to practice the claimed invention.

Therefore, it is respectfully submitted that neither Thomas nor the secondary references suggest the invention as a whole, as set out in claims 3-7, 12, 13, 26, 29, 30, 32 and 34-39.

For either or both of the foregoing reasons, it is respectfully requested that the rejection under 35 U.S.C. § 103 be withdrawn and claims 3-7, 12, 13, 26, 29, 30, 32 and 34-39 be allowed.

IV. Claims Rejected Under 35 U.S.C. § 112

Claims 22, 25, 27, 28, 31 and 33 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the

breadth of the claims *In re Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986); *In re Wands*, 8 USPQ 2d 1400, 1404 (Fed. Cir. 1988).

Each of the rejected claims lists a number of sequences from which the CETP immunogen of the present invention can be made.

Here, as in *Wands*, undue experimentation would not be required to practice the invention. The instant disclosure provides considerable direction and guidance on how to practice the claimed invention and presents examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known. See *Wands*, 8 USPQ 2d at 1406. Furthermore, Applicants have stated that the examples given will accomplish the claimed methods, or form the claimed products. The Examiner has not rebutted Applicants' contention, but rather has presented a reference (*Donnelly*, above) which shows that DNA vaccines are simple and effective. As mentioned above, the *Eck and Wilson* reference is concerned primarily with gene transfer "ultimately corrects a deficiency" (Eck and Wilson, page 78). Finally, the *Eck and Wilson* reference has an uncertain date, but certainly dates from a time prior to 1996, the date of the 9th edition of Goodman and Gilman's The Pharmacological Basis of Therapeutics. No references cited in *Eck and Wilson* have a date subsequent to 1994. Therefore, based upon the scope of the reference, and the uncertain date of the reference, it would be improper to characterize the state of the art based upon this particular reference. It is therefore respectfully requested that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn, and claims 22, 25, 27, 28, 31 and 33 be passed to issue.

V. Claims Rejected Under the Judicially Created Doctrine of Obviousness-type Double Patenting

Claims 3-7, 12, 13 and 22-39 stand rejected under the judicially created doctrine of obviousness-type double patenting over copending Application serial number 08/934,367 (claims 2-7, 8-11 and 15-31).

A provisional terminal disclaimer is filed herewith. It is believed that this disclaimer overcomes the double patenting rejection.

Claims 23 and 24, are subject only to this double patenting rejection. Claims 23 and 24 have been rewritten to be in independent form, including all of the limitations of the base claim and any intervening claims. Thus claim 23 depended from claim 13, which depends from claim 12 which in turn depends from claim 3. Therefore, claim 23 as amended contains all of the limitations of claims 13, 12, and 3. Likewise, claim 24 depended from claim 6, which in turn depends from claim 3. Therefore, claim 24 as amended contains all of the limitations of claims 6 and 3.

VI. Improperly Dependent Claim

Claim 28 was rejected as being improperly dependent upon a later independent claim. Upon indication of allowability of the relevant claims, claim 28 will be appropriately renumbered.

VII. New Claims

New claims 40 and 41 are rewritten versions of amended claims 23 and 24 with the following changes:

Claim 40 is rewritten claim 23, with fewer than all of the limitations of claim 13, but including all of the limitations of claim 32.

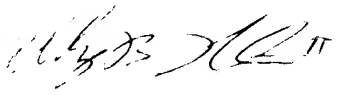
Claim 41 is claim 24 rewritten in independent form to include all of the limitations of claims 24, 6, and 3 (from which claim 24 depends) with the further limitation that the mammal is a human whose blood contains CETP.

New Claim 42 is written generically to cover both forms of inoculation (either peptides administered through inoculation directly or expressed *in vivo* through a DNA expression vector inoculation). Claims 43 and 45 are directed to the species of claim 42 wherein the DNA expression vector provides the CETP immunogen polypeptide. Claim 44 is directed to the species of claim 42 wherein said antigenic carrier is of Hepatitis B core protein. Claims 46 is dependent upon claim 42, and 47 is dependent upon claim 46. Both claims 46 and 47 include the limitation of human CETP immunogens, with claim 47 providing specific SEQ ID NOs comprising human CETP amino acid residues.

Conclusion

The claims of this application are now believed to be allowable, and it is respectfully requested that the case be passed to issue. Should the Examiner have questions or suggestions, she is requested to call applicants' undersigned attorney.

Respectfully submitted,



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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:. Needleman et al. GROUP ART UNIT: 1646

SERIAL NO.: 09/386,591 EXAMINER: Janet L. Andres

FILED: August 31, 1999 DOCKET NO.: 7919

FOR: AN IMMUNOLOGICAL PROCESS AND CONSTRUCTS FOR INCREASING THE HDL CHOLESTEROL CONCENTRATION BY DNA VACCINATION

AMENDMENT C
VERSIONS WITH MARKINGS
TO SHOW CHANGES MADE

3. A process for increasing the concentration of HDL cholesterol in the blood of a mammal whose blood contains cholesteryl ester transfer protein (CETP) that comprises the steps of:

(a) immunizing said mammal with an inoculum containing a vehicle in which is dissolved or dispersed a recombinant DNA molecule comprising a DNA sequence that contains (i) a sequence encoding a CETP immunogen linked to (ii) a promoter sequence that controls the expression of said CETP immunogen DNA sequence in said mammal, said CETP immunogen comprising an antigenic carrier of hepatitis B core protein to which is covalently bonded one or more immunogenic polypeptides comprising a CETP amino acid residue sequence of about 10 to about 30 residues; and

(b) maintaining said immunized mammal for a time period sufficient for said CETP immunogen to be expressed and for the production of antibodies that bind to CETP and lessen the transfer of cholesteryl esters from HDL, thereby

increasing the HDL concentration. 4. The process according to claim 3 wherein said immunizing step is repeated.

5. The process according to claim 3 wherein said immunizing step is repeated at intervals of about 3 to about 6 months until the HDL cholesterol value in the blood of said mammal is increased by about 10 percent or more relative to the HDL cholesterol value prior to said first immunization step.

6. (amended) The process according to claim 3 wherein said recombinant DNA molecule encodes human CETP as at least one of said one or more immunogenic polypeptides.

7. (amended) The process according to claim 3 wherein said recombinant DNA molecule encodes rabbit CETP as at least one of said one or more immunogenic polypeptides.

12. (three times amended) The process according to claim 3 wherein said antigenic carrier is fused to both the amino-terminus and carboxy-terminus of said immunogenic polypeptides, thereby forming an encoded fusion protein.

13. The process according to claim 12 wherein said encoded fusion protein is comprised of an immunogenic polypeptide having a length of about 10 to about 30 amino acid residues that are fused to an amino-terminal flanking sequence and a carboxy-terminal flanking sequence, wherein

(a) said amino-terminal flanking sequence consists essentially of about 10 to about 20 amino acid residues having an amino acid residue sequence of the hepatitis B core protein (HBcAg) from about position 1 to about position 35, and said carboxy-terminal sequence consists essentially of about 120 to about 160 amino acid

residues having an amino acid residue sequence of HBcAg from about position 10 about position 183, or

(b) said amino-terminal flanking sequence consists essentially of about 70 to about 90 residues having the amino acid residue sequence of HBcAg from about position 1 to about position 90, and said carboxy-terminal flanking sequence consists essentially of about 65 to about 85 amino acid residues having the amino acid residue sequence of HBcAg from about position 80 to about position 183.

22. (amended) The process according to claim 3 wherein at least one of said one or more immunogenic polypeptides is of a sequence independently selected from the group consisting of SEQ ID NOs: 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 29, 32, 33, 34, 35, 36, 37 and 50.

23. (amended) [The process according to claim 13]

A process for increasing the concentration of HDL cholesterol in the blood of a mammal whose blood contains cholesteryl ester transfer protein (CETP) that comprises the steps of:

(a) immunizing said mammal with an inoculum containing a vehicle in which is dissolved or dispersed a recombinant DNA molecule comprising a DNA sequence that contains (i) a sequence encoding a CETP immunogen linked to (ii) a promoter sequence that controls the expression of said CETP immunogen DNA sequence in said mammal, said CETP immunogen comprising an antigenic carrier of hepatitis B core protein to which is covalently bonded one or more immunogenic polypeptides comprising a CETP amino acid residue sequence of about 10 to about 30 residues, wherein said one or more immunogenic polypeptides are of a sequence selected from the

group consisting of SEQ ID NOs: 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 29, 32, 33, 34, 35, 36, 37 and 50,wherein said antigenic carrier is fused to both of the amino-terminus of at least one of said one or more immunogenic polypeptides and the carboxy-terminus of at least one of said one or more immunogenic polypeptides, thereby forming an encoded fusion protein, wherein said encoded fusion protein is fused to an amino-terminal flanking sequence and a carboxy-terminal flanking sequence, wherein

(1) said amino-terminal flanking sequence consists essentially of about 10 to about 20 amino acid residues having an amino acid residue sequence of the hepatitis B core protein (HBcAg) from about position 1 to about position 35, and said carboxy-terminal sequence consists essentially of about 120 to about 160 amino acid residues having an amino acid residue sequence of HBcAg from about position 10 about position 183, or

(2) said amino-terminal flanking sequence consists essentially of about 70 to about 90 residues having the amino acid residue sequence of HBcAg from about position 1 to about position 90, and said carboxy-terminal flanking sequence consists essentially of about 65 to about 85 amino acid residues having the amino acid residue sequence of HBcAg from about position 80 to about position 183; and

(b) maintaining said immunized mammal for a time period sufficient for said CETP immunogen to be expressed and for the production of antibodies that bind to CETP and lessen the transfer of cholesteryl esters from HDL, thereby increasing the HDL concentration.

24. (amended) [The process according to claim 6 wherein] A process for increasing the concentration of HDL cholesterol in the blood of a mammal

whose blood contains cholesteryl ester transfer protein (CETP) that comprises the steps of:

(a) immunizing said mammal with an inoculum containing a vehicle in which is dissolved or dispersed a recombinant DNA molecule comprising a DNA sequence that contains (i) a sequence encoding a human CETP immunogen, said encoded human CETP immunogenic polypeptide [comprises] comprising a sequence selected from the group consisting of SEQ ID NOs: 8-13 and 29 linked to (ii) a promoter sequence that controls the expression of said CETP immunogen DNA sequence in said mammal, said CETP immunogen comprising an antigenic carrier of hepatitis B core protein to which is covalently bonded one or more immunogenic polypeptides comprising a CETP amino acid residue sequence of about 10 to about 30 residues; and

(b) maintaining said immunized mammal for a time period sufficient for said CETP immunogen to be expressed and for the production of antibodies that bind to CETP and lessen the transfer of cholesteryl esters from HDL, thereby increasing the HDL concentration.

25. (amended) The process according to claim 7 wherein said encoded rabbit CETP immunogenic polypeptide comprises a sequence selected from the group consisting of SEQ ID NOs: 2-7 and 50.

26. (amended) The process according to claim 3 wherein said recombinant DNA molecule encodes monkey CETP as at least one of said one or more immunogenic polypeptides.

27. (amended) The process according to claim 26 wherein said at least one encoded monkey CETP immunogenic polypeptide comprises a sequence selected from the group consisting of SEQ ID NOs: 32-36 and 37.

28. (amended) The inoculum according to claim 35 wherein at least one of said one or more immunogenic polypeptides is of a sequence selected from the group consisting of SEQ ID NOs: 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 12, 13, 29, 32, 33, 34, 35, 36, 37 and 50.

29. A recombinant DNA molecule comprising a DNA sequence that contains (i) a sequence encoding a cholesteryl ester transfer protein (CETP) immunogen linked to (ii) a promoter sequence that controls the expression of said CETP immunogen DNA sequence in a mammal, said CETP immunogen being comprised of an exogenous antigenic carrier of hepatitis B core protein to which is covalently bonded one or more immunogenic polypeptides of a CETP amino acid residue sequence of about 10 to about 30 residues.

30. The recombinant DNA according to claim 29 wherein said promoter sequence is a cytomegalovirus immediate-early promoter sequence.

31. (twice amended) The recombinant DNA according to claim 30 wherein at least one of said one or more immunogenic polypeptides [are] is of a sequence independently selected from the group consisting of SEQ ID NOs: 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 29, 32, 33, 34, 35, 36, 37 and 50.

32. The process according to claim 13 wherein the number of amino acid residues present in said encoded immunogenic polypeptide is about equal in number to the number of amino acid residues absent from said HBcAg amino acid residue

sequence between the carboxy-terminal residue position of said amino terminal flanking sequence and the amino-terminal residue of said carboxy-terminal flanking sequence.

33. The process according to claim 3 wherein said encoded immunogenic polypeptide has the amino acid residue sequence of SEQ ID NOs: 29 or 50.

34. The process according to claim 3 wherein said immunization is carried out by injecting said inoculum into muscle or skin of said mammal.

35. An inoculum that comprises a recombinant DNA molecule comprising a DNA sequence that contains (i) a sequence encoding a CETP immunogen linked to (ii) a promoter sequence that controls the expression of said CETP immunogen DNA sequence in a mammal, said recombinant DNA molecule being dissolved or dispersed in an effective amount in a vehicle, said CETP immunogen comprising an antigenic carrier of hepatitis B core protein to which is covalently bonded one or more immunogenic polypeptides comprising a CETP amino acid residue sequence of about 10 to about 30 residues.

36. The inoculum of claim 35 wherein the concentration of said DNA encoding said CETP immunogen is about 0.05 μg/ml to about 20 mg/ml.

37. The inoculum of claim 35 wherein said vehicle is phosphate-buffered saline.

38. The inoculum of claim 35 wherein said vehicle is isotonic sucrose.

39. The inoculum of claim 35 wherein said DNA is complexed with liposomes.

New Claims

Please add the following claims 40-47:

40. A process for increasing the concentration of HDL cholesterol in the blood of a mammal whose blood contains cholesteryl ester transfer protein (CETP) that comprises the steps of:

(a) immunizing said mammal with an inoculum containing a vehicle in which is dissolved or dispersed a recombinant DNA molecule comprising a DNA sequence that contains (i) a sequence encoding a CETP immunogen, said encoded CETP immunogenic polypeptide linked to (ii) a promoter sequence that controls the expression of said CETP immunogen DNA sequence in said mammal, said CETP immunogen comprising an antigenic carrier of hepatitis B core protein to which is covalently bonded one or more immunogenic polypeptides comprising a CETP amino acid residue sequence of about 10 to about 30 residues, wherein the number of amino acid residues present in said encoded immunogenic polypeptide is about equal in number to the number of amino acid residues absent from said HBcAg amino acid residue sequence between the carboxy-terminal residue position of said amino terminal flanking sequence and the amino-terminal residue of said carboxy-terminal flanking sequence; and

(b) maintaining said immunized mammal for a time period sufficient for said CETP immunogen to be expressed and for the production of antibodies that bind to CETP and lessen the transfer of cholesteryl esters from HDL, thereby increasing the HDL concentration.

41. A process for increasing the concentration of HDL cholesterol in the blood of a human whose blood contains cholesteryl ester transfer protein (CETP) that

comprises the steps of:

(a) immunizing said human with an inoculum containing a vehicle in which is dissolved or dispersed a recombinant DNA molecule comprising a DNA sequence that contains (i) a sequence encoding a CETP immunogen, said encoded human CETP immunogenic polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs: 8-13 and 29 linked to (ii) a promoter sequence that controls the expression of said CETP immunogen DNA sequence in said mammal, said CETP immunogen comprising an antigenic carrier of hepatitis B core protein to which is covalently bonded one or more immunogenic polypeptides comprising a CETP amino acid residue sequence of about 10 to about 30 residues; and

(b) maintaining said immunized mammal for a time period sufficient for said CETP immunogen to be expressed and for the production of antibodies that bind to CETP and lessen the transfer of cholesteryl esters from HDL, thereby increasing the HDL concentration.

42. A process for increasing the concentration of HDL cholesterol in the blood of a mammal whose blood contains cholesteryl ester transfer protein (CETP) that comprises the steps of:

(a) causing to be present in said mammal a CETP immunogen in an amount effective to raise antibodies in said mammal to CETP endogenous to said mammal comprising an antigenic carrier polypeptide covalently bonded to at least one immunogenic polypeptide of about 10 to about 30 residues comprising a CETP amino acid residue sequence, said CETP amino acid residue sequence corresponding to a sequence of CETP endogenous to said mammal; and

(b) maintaining said mammal for a time period sufficient for the production of antibodies that bind to CETP and lessen the transfer of cholesteryl esters from HDL, thereby increasing the HDL concentration.

43. The process of claim 42 wherein said CETP immunogen is expressed in said mammal through an appropriate recombinant expression vector.

44. The process of claim 42 wherein said antigenic carrier is of Hepatitis B core protein.

45. The process of claim 43 wherein said recombinant expression vector is injected intramuscularly in said mammal.

46. The process of claim 42 wherein said mammal is a human, and said CETP amino acid residue sequence corresponds to a human CETP residue sequence.

47. The process of claim 46 wherein said human CETP residue sequence is selected from the group consisting of SEQ ID NOs: 8-13 and 29.